Use of Systemic Therapy Concurrent With Cranial Radiotherapy for Cerebral Metastases of Solid Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Brain metastases • Radiotherapy • Systemic therapy • Molecular targeted agents • Monoclonal antibodies • Toxicity

ABSTRACT

The incidence of brain metastases of solid tumors is increasing. Local treatment of brain metastases is generally straightforward: cranial radiotherapy (e.g., whole-brain radiotherapy or stereotactic radiosurgery) or resection when feasible. However, treatment becomes more complex when brain metastases occur while other metastases, outside of the central nervous system, are being controlled with systemic therapy (chemotherapeutics, molecular targeted agents, or monoclonal antibodies). It is known that some anticancer agents can increase the risk for neurotoxicity when used concurrently with radiotherapy. Increased neurotoxicity decreases quality of life, which is undesirable in this predominantly palliative patient group. Therefore, it is of utmost importance to identify the compounds that should be temporarily discontinued when cranial radiotherapy is needed.

This review summarizes the (neuro)toxicity data for combining systemic therapy (chemotherapeutics, molecular targeted agents, or monoclonal antibodies) with concurrent radiotherapy of brain metastases. Because only a limited amount of high-level data has been published, a risk assessment of each agent was done, taking into account the characteristics of each compound (e.g., lipophilicity) and the microenvironment of brain metastasis. The available trials suggest that only gemcitabine, erlotinib, and vemurafenib induce significant neurotoxicity when used concurrently with cranial radiotherapy. We conclude that for most systemic therapies, the currently available literature does not show an increase in neurotoxicity when these therapies are used concurrently with cranial radiotherapy. However, further studies are needed to confirm safety because there is no high-level evidence to permit definitive conclusions. The Oncologist 2017;22:222–235

Implications for Practice: The treatment of symptomatic brain metastases diagnosed while patients are receiving systemic therapy continues to pose a dilemma to clinicians. Will concurrent treatment with cranial radiotherapy and systemic therapy (chemotherapeutics, molecular targeted agents, and monoclonal antibodies), used to control intra- and extracranial tumor load, increase the risk for neurotoxicity? This review addresses this clinically relevant question and evaluates the toxicity of combining systemic therapies with cranial radiotherapy, based on currently available literature, in order to determine the need to and interval to interrupt systemic treatment.

INTRODUCTION

Systemic treatment options for metastasized solid tumors have increased [1–6]. Thus, long-term progression-free survival can sometimes be achieved, especially when a driver oncogene in the tumorigenesis of a specific tumor can be targeted, such as BRAF V600E in melanoma. Moreover, radical treatment for patients with oligometastatic disease has become an accepted treatment modality [7]. With a growing number of long-term cancer survivors, brain metastases are frequently observed, especially in patients with non-small cell lung cancer (NSCLC), breast cancer, melanoma, and renal cell carcinoma (RCC) [8].

Some systemic treatment schedules (chemotherapeutics, targeted agents, and monoclonal antibodies) show intracranial response and/or stabilization of brain metastases [9, 10]. Contrary to traditional chemotherapeutic agents, recently developed targeted agents show the potential to cross the blood-brain barrier (BBB). These targeted agents may be able to...
control brain metastases, especially when the brain metastases are relatively small and asymptomatic [1]. However, despite initial responses, brain metastases often progress during systemic treatment. Traditionally, whole-brain radiotherapy (WBRT) is the cornerstone of the treatment of symptomatic multiple (four or more) brain metastases. The use of partial-brain radiation therapy techniques, including but not limited to stereotactic radiosurgery (SRS) and stereotactic radiotherapy, has increased and is the preferred initial treatment option in patients with a limited number of (one to three) brain metastases smaller than 4 cm [2]. Depending on national guidelines, number, size, and leptomeningeal spread of the brain metastases, cranial radiotherapy is the treatment modality of choice.

Some chemotherapeutics and targeted agents have shown to be radiosensitizing for healthy brain tissue, which may increase the risk for complications. These complications have mainly been described in the extracranial setting (e.g., bleeding, bowel perforation, radionecrosis) and resulted in severe morbidity and impaired quality of life [11–13].

To minimize the risk for neurotoxicity, systemic therapies are often discontinued during cranial radiotherapy. However, the disadvantage of discontinuation is a potential tumor flare of extracranial disease. Ninety-seven percent of systemically administered oncolytic drugs is eliminated from the blood after 5 times the half-life \( t_{1/2} \). Because of the long \( t_{1/2} \) of most targeted agents (or their active metabolites) and monoclonal antibodies, this would mean a long period (weeks to months) of discontinuation when this level of elimination is pursued, which is undesirable in the control of extracranial tumor load. Additionally, 97% of drug excretion might not be sufficient to abolish the metabolic activity of these agents in brain metastases.

The aim of this review is to determine which of the commonly used systemic therapies can be safely continued during cranial radiotherapy and which should be discontinued, based on the currently available literature. We discuss the chemotherapeutics, targeted agents, and monoclonal antibodies that are most commonly used in the subset of solid tumors that most frequently metastasize to the brain.

**MATERIALS AND METHODS**

Systemic therapies that are commonly used in the treatment of tumors that metastasize to the brain were selected for inclusion. The search was conducted on papers describing the combination of these systemic agents and cranial radiotherapy of cerebral metastases of solid tumors. Additional literature describing the ability of the systemic therapy to penetrate the BBB and pharmacological characteristics was gathered as supportive information. With these data, a narrative review was executed, as this is the best review format that can be obtained considering the available information.

**Inclusion and Exclusion Criteria**

Papers describing the combination of cranial radiotherapy and one of the selected systemic therapies and having (neuro)toxicity as an outcome measure were eligible for inclusion. All types of articles (including reviews; case reports; and phase I, II, and III studies) were included.

Papers describing the treatment of primary brain tumors were excluded. All non-English-language articles were excluded.

Additional literature was searched on combined chemotherapeutic schedules because literature on separately used chemotherapeutics was very scarce. However, this was not part of the main search strategy.

**Identification of Studies**

The literature search was conducted independently by two researchers (M.V. and H.M.) up to June 2015 using the databases PubMed, MEDLINE, Cochrane, and Web of Science. References from the included studies were also reviewed for eligible literature. The complete search strategy can be found in the supplemental online data (Appendix A).

**Study Selection**

Studies were initially selected on the basis of title; further selection took place according to the abstracts. For articles found to be eligible, the whole article was read. Eligibility was assessed by two reviewers (M.V. and H.M.). Disagreements were resolved by consensus.

**Data Extraction**

From the included papers, data were extracted on (a) trial characteristics; (b) treatment schedule used; and (c) the described neurotoxicity, methods of evaluating toxicity, assessment of quality of life (QoL) and neurocognition, and follow-up characteristics.

**RESULTS**

An overview of the trial characteristics can be found in the supplemental online data (Appendix B). Working mechanisms of the discussed systemic therapies are reported in Appendix C of the supplemental online data. Table 1 describes pharmacological characteristics of the systemic agents discussed in this review. Table 2 describes all reported neurotoxicity.

A total of 2,172 records were identified by using the search strategy (Appendix A). In the end, 37 articles were included in the review. Figure 1 provides an overview of the complete selection process.

**Combination of Radiotherapy and Chemotherapy**

**Antimetabolites: Capecitabine/5-Fluorouracil and Gemcitabine**

Two studies describe toxicity (Table 2) of capecitabine used concurrently with cranial radiotherapy. One study reported overall mild toxicity and no high-grade neurotoxicity [14]. A second study, a phase II trial, in which capecitabine was combined with WBRT followed by sunitinib, closed early because of low efficacy and excessive toxicity, although no high-grade neurotoxicity was mentioned [15]. Neurocognitive impairment and QoL, both salient endpoints, were not separately scored in these studies.

Two trials investigated toxicity (Table 2) for the combination of gemcitabine and cranial radiotherapy. A phase I trial reported dose-limiting toxicity at the highest dose level (70 mg/m² twice weekly) to be grade IV neutropenia. No significant nonhematological toxicities were observed at any dose level. Moreover, no deterioration in mental function was observed by the Folstein test [16]. In another phase I trial, dose-limiting neurotoxicity was observed, at a dose of 700 mg/m², consisting of grade III seizures and grade II muscle weakness [17]. Neither study scored for QoL. Additionally, gemcitabine-induced radiation recall, a serious inflammatory reaction often leading to necrosis, has been described. Radiation recall reactions were seen in the central
<table>
<thead>
<tr>
<th>Oncolytic</th>
<th>( t_{1/2} )</th>
<th>Main excretory pathway % (within timeframe)</th>
<th>Prodrug</th>
<th>Active metabolites</th>
<th>Intact BBB penetration MW and lipophilicity</th>
<th>Fraction protein unbound CSF/plasma concentration or % penetration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>45–70 min</td>
<td>R 84% 24 h; 96% 7 d</td>
<td>Yes</td>
<td>5’-DFCR, 10 min; 5’-DFUR, 20 min; fluorouracil, within 45 min, mainly at tumor site; further metabolized to active metabolites dFdUMP and FUTP and to inactive metabolite FBAL</td>
<td>Yes; MW 359 g/mol; XLogP3 = 0.6</td>
<td>Breast cancer brain metastases/serum ratio capecitabine, 0.28% (0.031%–0.81%); 5-FU, 5.64% (1.67%–12.9%)</td>
<td>[81–84]</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2–3 h free ultrafiltrable platinum and carboplatin; 4–6 d total platinum</td>
<td>R 71% 24 h</td>
<td>No</td>
<td>Carboplatin undergoes intracellular hydrolysis to form reactive platinum complexes; 5.8 ± 1.6 d (total platinum, including protein-bound fraction)</td>
<td>Limited; MW 371 g/mol</td>
<td>Low tissue-to-blood ratio</td>
<td>[85–87]</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>23–54 min free ultrafiltrable platinum; 2–5 d total platinum</td>
<td>R &gt; 90% 25% 24 h</td>
<td>Platinum analog</td>
<td>Not readily; MW 300 g/mol</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>11 h</td>
<td>B/F 80% 48 h</td>
<td>No</td>
<td>NA</td>
<td>Limited, relatively low levels, but large interpatient variation; MW 808 g/mol; XLogP3 = 1.6</td>
<td>Fraction unbound in CSF 67%–103%; ratio total (CSF to plasma) 0.01%–0.6%, protein bound, 0.1%–9% (~IC50)</td>
<td>[88]</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.7–1.6 h (infusion &lt;30 min)</td>
<td>R 92%–98% 1 wk 89% as dFdU</td>
<td>Yes</td>
<td>dFdC undergoes intracellular activation to pharmacologically active dFdCDP and dFdCTP and metabolic inactivation to dFdU metabolite</td>
<td>Unknown; MW 300 g/mol</td>
<td>Believed to cross, if disrupted</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>2.5 h (3-h infusion 175 mg/m²) extravascular distribution: longer terminal ( t_{1/2} )</td>
<td>B/F 71%</td>
<td>No</td>
<td>NA</td>
<td>Limited; MW 854 g/mol; XLogP3 = 2.5</td>
<td>Brain tumor tissue concentrations were in therapeutic range in 3 patients but low in another patient; difference possibly related to BBB disruption; metastatic brain tumors had higher paclitaxel concentrations in the tumor center (1.93-fold, ( p = .10 )) and in tumor periphery (2.46-fold, ( p = .039 )) compared with primary brain tumors</td>
<td>[89, 90]</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>40–60 h</td>
<td>F 61%</td>
<td>No</td>
<td>Desethyl metabolite SU12662 (similar potency to that of sunitinib) 80–110 h</td>
<td>Seems able to cross BBB in small amounts; MW 398 g/mol; XLogP3 = 2.6</td>
<td>Only animal (mouse) studies available</td>
<td>[105]</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25–48 h</td>
<td>F 77%</td>
<td>No</td>
<td>Pyridine-N-oxide (similar potency to that of sorafenib)</td>
<td>Limited, based on animal studies; MW 465 g/mol; XLogP3 = 4.1</td>
<td>Only animal (mouse/monkey) studies available: rhesus monkeys; CSF penetration of sorafenib was 0.02% and 3.4% after correcting for plasma protein binding</td>
<td>[106]</td>
</tr>
</tbody>
</table>

(continued)
nervous system, skin, gastrointestinal tract, and lymphatic and musculoskeletal systems. The time between initiation of radiation and recall of the radiation phenomenon ranged from 3 weeks to 8 months from the time gemcitabine was initiated. The usual dosage of gemcitabine in these cases was 1,000 mg/m² given weekly [18–20].

Platinum Analogs: Cisplatin and Carboplatin
One study described the toxicity (Table 2) of cisplatin combined with cranial radiotherapy. In this study, 4 of 14 patients had possible central nervous system toxicity, categorized as neurological deterioration and seizure. However, in all 4 patients other possible reasons for the transient neurologic deterioration were present, such as tapering of corticosteroids [21].

<table>
<thead>
<tr>
<th>Oncolytic</th>
<th>( t_{1/2} )</th>
<th>Main excretory pathway % (within timeframe)</th>
<th>Prodrug</th>
<th>Active metabolites</th>
<th>Intact BBB penetration MW and lipophilicity</th>
<th>Fraction protein unbound CSF/plasma concentration or % penetration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>36.2 h</td>
<td>B/F 90%</td>
<td>No</td>
<td>OSI-420 and OSI-413 present in plasma at levels &lt;10% of erlotinib and display similar pharmacokinetics as erlotinib</td>
<td>Yes, partially; MW 393 g/mol; ( \text{XLog}P_3 = 3.3 )</td>
<td>2.0% ± 0.5% in combination with cisplatin/pemetrexed; erlotinib only 2.3% ± 0.2% – 2.77%–5.1% also 4.4% ± 3.2% found without WBRT; pulsatile (intermittent) erlotinib 1,000–1,500 mg weekly; penetration rate 1.15% but CSF concentration &gt; IC(_{50})</td>
<td>[83, 91–95]</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>30.5–41 h</td>
<td>F 86%</td>
<td>No</td>
<td>0-desmethyl-gefitinib (1/14 the potency of gefitinib)</td>
<td>Yes, partially; MW 447 g/mol; ( \text{XLog}P_3 = 4.1 )</td>
<td>Mean ratio CSF/total plasma concentration 1.3% ± 0.7%; CNS penetration closer to 50% when one accounts for available free drug; penetration rate in CSF 1.13% ± 0.36%. Concentration in CSF distinctly less than its IC(_{50})</td>
<td>[87, 91, 92, 96, 97]</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>24 h</td>
<td>F up to 67%</td>
<td>No</td>
<td>NA: activity not characterized</td>
<td>Limited; MW 581 g/mol; ( \text{XLog}P_3 = 5.1 )</td>
<td>~50 fold; uptake demonstrated in nonirradiated breast cancer brain metastatic tissue (pulsatile lapatinib): breast cancer brain metastases: serum ratio: 0.19%–9.8%</td>
<td>[83, 84, 98, 107]</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>30–120 h</td>
<td>F 94%</td>
<td>No</td>
<td>NA, or activity not characterized yet</td>
<td>Generally limited; MW 490 g/mol; ( \text{XLog}P_3 = 5.0 )</td>
<td>CSF: plasma concentration ratio 0.98% ± 0.84%</td>
<td>[99–101]</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>14.7–15.6 d</td>
<td>TMD</td>
<td>No</td>
<td>NA</td>
<td>Unlikely; however, activated T cells might do so; MW 148 kDa</td>
<td>Penetration unlikely based on MW</td>
<td>[105]</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>28–38 d</td>
<td>(washout till 27 wk)</td>
<td>TMD</td>
<td>NA</td>
<td>Without a compromised BBB, trastuzumab is thought to have limited access</td>
<td>Penetration unlikely based on MW</td>
<td>[102, 107]</td>
</tr>
<tr>
<td>Bevacuzimab</td>
<td>18–20 d; shortest for women</td>
<td>TMD</td>
<td>No</td>
<td>NA</td>
<td>Unlikely, but possible (VEGF might manipulate BBB integrity); MW 149 kDa</td>
<td>Penetration unlikely based on MW</td>
<td>[103, 104]</td>
</tr>
</tbody>
</table>

Abbreviations: 5'-DFCR, 5'-deoxy-5-fluorocytidine; 5'-DFUR, 5'-deoxy-5-fluorouridine; BBB, blood-brain-barrier; B/F, biliary and/or fecal excretion; CSF, cerebrospinal spinal fluid; d, day(s); dFdC, 2',2'-difluoro-2'-deoxycytidine; dFdCDP, 2',2'-difluoro-2'-deoxycytidin diphosphate; dFdCTP, 2',2'-difluoro-2'-deoxycytidine; dFdU, 2',2'-difluorodeoxyuridine; FBAL, α-fluoro-β-alanine; FdUMP, 5-fluorodeoxy-uridine-5-monophosphate; FUTP, fluorouridine-5-triphosphate; h, hour(s); IC\(_{50}\), half maximum inhibitory concentration (measure of how much of a drug is needed to inhibit a certain biological process by half); MW, molecular weight; NA, not available; R, renal excretion; \( t_{1/2} \), half-life; TMD, target-mediated deposition; VEGF, vascular endothelial growth factor; WBRT, whole-brain radiation therapy.
### Table 2. Overview of reported toxicity with concurrent use of systemic therapies and cerebral radiotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author, year</th>
<th>Reported neurotoxicity</th>
<th>Method of evaluating toxicity</th>
<th>Follow-up toxicity characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Chargari et al., 2009</td>
<td>Grade I nausea and headache. No severe neurotoxicity.</td>
<td>RTOG radiation morbidity scoring system</td>
<td>Gadolinium-enhanced MRI or CT, 6 wk after treatment and in case of neurologic symptoms. Medical interview and clinical examination every 3 mo.</td>
</tr>
<tr>
<td></td>
<td>Niravath et al., 2015</td>
<td>No significant neurotoxicity</td>
<td>No described</td>
<td>Not described</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Maraveyas et al., 2005</td>
<td>No significant neurotoxicity at any dose level</td>
<td>WHO scale. Folstein mini-mental test at baseline, weekly during treatment and every 4 wk thereafter until progression.</td>
<td>CT or MRI of the brain 4 wk after treatment</td>
</tr>
<tr>
<td>Huang et al., 2007</td>
<td></td>
<td>Seizures (grade III), muscle weakness (grade II) at 700 mg/m²</td>
<td>CTC scale</td>
<td>MRI 1 mo after treatment, every 2 mo until progression or death. MMSE weekly during treatment, every 2 mo thereafter until progression.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Stewart et al., 1982</td>
<td>Neurological deterioration and seizures (possibly due to other reasons than toxic effect)</td>
<td>Weekly blood counts. CT, audiography, and EEG as clinically needed.</td>
<td>Weekly blood counts. CT, audiography, and EEG as clinically needed.</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Guerrieri et al., 2004</td>
<td>Not suitable for evaluation because of poor accrual and early closure of trial. No difference between WBRT and WBRT + carboplatin group</td>
<td>Neurological function status</td>
<td>CT or MRI of brain 6 wk after treatment. WHO performance status, neurological function status, presence/absence of neurological symptoms.</td>
</tr>
<tr>
<td><strong>Chemotherapy schedules</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin, vinorelbine, ifosfamide</td>
<td>Quantin et al., 1999</td>
<td>Early dementia (n = 1)</td>
<td>Canadian Neurological Scale</td>
<td>Not described</td>
</tr>
<tr>
<td></td>
<td>Quantin et al., 2010</td>
<td>No neurotoxicity reported</td>
<td>Neurological evaluation</td>
<td>Not described</td>
</tr>
<tr>
<td>Cisplatin, vindisine, mitomycin</td>
<td>Furuse et al., 1997</td>
<td>No neurotoxicity reported</td>
<td>WHO toxicity score</td>
<td>Weekly evaluation toxicity, neurological function classification by Borgelt, CT 8 wk after treatment and if neurological symptoms occurred</td>
</tr>
<tr>
<td>Pemetrexed, cisplatin or carboplatin</td>
<td>Chargari et al., 2013</td>
<td>Unexplained encephalopathy due to miliary metastasis (n = 1), no increased neurotoxicity</td>
<td>CTCAE version 3.0</td>
<td>Gadolinium-enhanced MRI or contrast-enhanced CT 8 wk after treatment and if neurological symptoms occurred. Clinical examination, medical examination.</td>
</tr>
<tr>
<td></td>
<td>Dinglin et al., 2013</td>
<td>Headache grade III (n = 3), nausea/vomiting grade III (n = 8)</td>
<td>NCI CTC version 2.0</td>
<td>Medical history and physical examination every 6 wk</td>
</tr>
<tr>
<td>Cisplatin, vinorelbine</td>
<td>Robinet et al., 2001</td>
<td>Confusion (n = 1), coma (n = 2), seizures (n = 1), worsening Parkinson’s (n = 1)</td>
<td>WHO toxicity score</td>
<td>Not described</td>
</tr>
</tbody>
</table>
## Table 2. (continued)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author, year</th>
<th>Reported neurotoxicity</th>
<th>Method of evaluating toxicity</th>
<th>Follow-up toxicity characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin, etoposide</td>
<td>Chen et al., 2012</td>
<td>Grade III + IV nausea and vomiting (52.9%)</td>
<td>NCI CTC version 2.0</td>
<td>Medical history, physical examination, NCI CTC version 2.0</td>
</tr>
<tr>
<td>Cisplatin, paclitaxel with vinorelbine or gemcitabine</td>
<td>Cortes et al., 2003</td>
<td>Grade III neurotoxicity ($n = 1$)</td>
<td>WHO criteria</td>
<td>Physical examination, monitoring toxicity, CT</td>
</tr>
</tbody>
</table>

**TKI**

<table>
<thead>
<tr>
<th>TKI</th>
<th>Author, year</th>
<th>Reported neurotoxicity</th>
<th>Method of evaluating toxicity</th>
<th>Follow-up toxicity characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>Chung et al., 2012</td>
<td>Grade I–II bleeding (unspecified location) and fatigue. No grade III or higher toxicity.</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Wuthrick et al., 2011</td>
<td>Grade I headache and motor neuropathy, grade III fatigue, dysphagia and difficulty chewing, grade II and V seizure (due to progression of brain metastasis)</td>
<td>CTCAE version 3.0</td>
<td>History, physical examinations, and chemistry studies weekly during treatment and 1 mo after treatment. MRI or CT 1 mo after treatment and at regular follow-up appointments.</td>
<td></td>
</tr>
<tr>
<td>Sunitinib and/or sorafenib</td>
<td>Arneson et al., 2014</td>
<td>No high-grade neurotoxicity</td>
<td>Not described</td>
<td>Not described</td>
</tr>
<tr>
<td>Staehler et al., 2011</td>
<td>Asymptomatic grade II bleeding in tumor. Grade II convulsions. No grade III or higher neurotoxicity.</td>
<td>CTCAE version 3.0</td>
<td>CT and/or MRI every 12 wk</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Lind et al., 2009</td>
<td>Grade I–II headache. Grade I–III fatigue. No other neurotoxicity was reported.</td>
<td>CTCAE version 3.0</td>
<td>Toxicity assessment and clinical response at 1 wk and 2 wk of WBRT and at 2 wk, 4 wk, and 2 mo and then every 2 mo thereafter. MRI/CT at 3-mo intervals.</td>
</tr>
<tr>
<td>Zhuang et al., 2013</td>
<td>No difference in toxicity between WBRT-only and WBRT + erlotinib groups. Grade I and II headache and dizziness.</td>
<td>CTCAE version 3.0</td>
<td>Whole-body examination at 1 mo and every 2–3 mo thereafter, including brain MRI, detailed medical history and physical examination</td>
<td></td>
</tr>
<tr>
<td>Welsh et al., 2013</td>
<td>No difference in neurotoxicity compared with historical control group. Grade I–III headache and grade I–II dizziness was reported.</td>
<td>CTCAE version 3.0</td>
<td>Medical history, physical examination, neurological examination, MMSE, blood tests, toxicity evaluation at 1 mo and every 3 mo thereafter. MRI every 3 mo. Cognitive function (Hopkins Verbal Learning Test-Revised, Trail Making Test Parts A and B and Multilingual Aphasia Examination Controlled Oral Word Association test) every 3 mo</td>
<td></td>
</tr>
<tr>
<td>Olmez et al., 2010</td>
<td>Mental status changes (category grade III–V), neurologic deterioration (category grade III–V)</td>
<td>NCI CTC version 3</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
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</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Wang et al., 2015</td>
<td>No reported neurotoxicity</td>
<td>CTCAE version 3.0</td>
<td>CT/MRI and clinical evaluation every 3 mo in first year and every 6 mo thereafter</td>
</tr>
<tr>
<td>Zeng et al., 2012</td>
<td>Headache, vomiting, and hypomnesia were more common in WBRT + gefitinib group than WBRT-only group (not significant)</td>
<td>NCI CTC version 2.0</td>
<td>Monthly toxicity evaluations. MRI every 2-3 mo until progression</td>
<td></td>
</tr>
<tr>
<td>Ma et al., 2009</td>
<td>Grade I–III nausea, vomiting, headache, and fatigue</td>
<td>NCI CTC</td>
<td>Weekly physical and neurological examinations during concurrent treatment</td>
<td></td>
</tr>
<tr>
<td>Pesce et al., 2012</td>
<td>2 grade II fatigue, 2 grade III fatigue, and 1 grade IV fatigue. One case of grade III nausea/vomiting.</td>
<td>CTCAE version 3.0</td>
<td>Cognitive function measured with MMSE and Trailmaking Test Part B</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Lin et al., 2013</td>
<td>Grade I–II headache, neuropathy, dizziness, insomnia, memory impairment, depression, and weakness. One grade III or higher seizure, no other neurotoxicity of grade III or higher reported</td>
<td>CTCAE version 3.0</td>
<td>CT/MRI every 8 wk. Weekly clinical assessment during WBRT and at beginning of each cycle thereafter.</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Schulze et al., 2014</td>
<td>Radiodermatitis</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Liebner et al., 2014</td>
<td>Symptomatic radionecrosis that required treatment</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
### Table 2. (continued)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Author, year</th>
<th>Reported neurotoxicity</th>
<th>Method of evaluating toxicity</th>
<th>Follow-up toxicity characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Silk et al., 2013</td>
<td>No increased neurotoxicity between RT alone and RT + ipilimumab. Intratumoral hemorrhage was reported.</td>
<td>Not mentioned</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mathew et al., 2013</td>
<td>No significant difference between SRS group and SRS + ipilimumab groups. Intratumoral hemorrhage was reported.</td>
<td>Not mentioned</td>
<td>Clinical investigation every 4 wk and MRI at 6 wk and every 12 wk thereafter</td>
<td></td>
</tr>
<tr>
<td>Gerber et al., 2015</td>
<td>Possibly more intratumoral bleeding, grade III cognitive change. Otherwise low-grade neurotoxicity (headache, dizziness, fatigue, nausea, visual changes, cognitive changes, and seizures)</td>
<td>CTCAE version 4.0</td>
<td>Weekly assessment of neurological symptoms</td>
<td></td>
</tr>
<tr>
<td>Tazi et al., 2015</td>
<td>Grade I–II hypopituitarism (1 case = 10%)</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiess et al., 2015</td>
<td>Grade III and IV CNS bleeding (from treated BM), grade III seizure. Otherwise low-grade neurotoxicity (headache, fatigue, cognitive changes, and neurological dysfunction)</td>
<td>CTCAE version 3.0</td>
<td>MRI 6-8 wk after SRS, then every 3 mo. Melanoma-specific graded prognostic assessment score</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Chargari et al., 2011</td>
<td>Headache, vertigo, and nausea (grade 1). No other neurotoxicity.</td>
<td>CTCAE version 3.0</td>
<td>MRI/CT 6 wk after treatment and in case of neurological symptoms. Clinical examination every 3 mo.</td>
</tr>
</tbody>
</table>

(continued)
### Combination of Radiotherapy and Targeted Agents

**Sunitinib and Sorafenib**
Four studies described the toxicity (Table 2) of sunitinib (25 mg once daily or 37.5 mg once daily or 50 mg once daily for 4 weeks on, 2 weeks off) and/or sorafenib (400 mg once or twice daily) combined with cranial radiotherapy. Three studies described no grade III or higher neurotoxicity. Neurocognition and QoL were not assessed [31–33]. One study showed grade III fatigue and grade III dysphagia and drooling/difficulty chewing. One patient died of grade V seizures, but this was attributed to progression of brain metastasis. No testing was done regarding neurocognition or QoL [34].

**Erlotinib**
Eight studies with concurrent use of erlotinib (100 mg or 150 mg once daily) and cranial radiotherapy were identified (Table 2). One study reported no high-grade neurotoxicity [35]. Another study reported 1 case (out of 50) with grade III headache. This study also evaluated neurocognition and found no statistical difference between the treatment group and a historical control group [36]. Four studies compared radiotherapy alone with radiotherapy combined with erlotinib. None of these trials reported a significant difference in neurotoxicity between the treatment arms [37–40]. QoL was assessed in one study (EuroQol EQ-5D questionnaire), and no significant difference was observed between the treatment groups [37]. One retrospective study found grade III–V mental status changes in three cases without clear etiology. No other neurotoxicity was reported. Neurocognition and QoL were not assessed [41]. A phase III study compared the combination of WBRT and SRS with or without erlotinib. In the erlotinib group, grade III neurotoxicity, including fatigue, muscle weakness, confusion, and ataxia; grade IV brain necrosis; and one grade V hemorrhagic stroke were found. A significant increase in overall toxicity was found when erlotinib was added to cranial radiotherapy. QoL (by performance status) was also negatively affected by the addition of erlotinib to cranial radiotherapy [42].

**Gefitinib**
Five studies described toxicity (Table 2) when gefitinib (250 mg once daily) was combined with cranial radiotherapy. One study reported no neurotoxicity [43]; however, another study reported few cases of grade III neurotoxicity [44]. Both reported an improvement in QoL (activities of daily living scoring or Functional Assessment of Cancer Therapy-Brain [FACT-Br]) after treatment with gefitinib and cranial radiotherapy. One retrospective study reported slightly more headache, vomiting, and hypomnesia, although not significantly so, in the concurrent-use group compared with the gefitinib-only group. The performance score did not differ between the groups before or after treatment [45]. Another retrospective study compared toxicity between radiotherapy with or without gefitinib and found no difference in adverse events. Neurocognition and QoL were not assessed [39]. A phase II study reported different levels of fatigue. Grade III nausea and vomiting were also reported. Neurocognition and QoL (Folstein test, Trail-making Test part B, and Quality of Life Questionnaire-Core 36 score) were stable before and after the treatment period [46].

**Lapatinib**
One study described the toxicity (Table 2) of lapatinib (maximum, 1,500 mg once daily) combined with cranial radiotherapy. This trial reported a seizure in one patient. No other grade III or higher neurotoxicity was reported. QoL was scored by using FACT-Br and showed a general decline of QoL after the treatment. However, only a limited number of patients could be tested both at baseline and after finishing treatment [47].

### Table 2. (continued)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Carlson et al., 2014</td>
<td>Increased symptomatic cerebral edema, Grade I–II headache, nausea, and vomiting. No grade III or higher toxicity.</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**Taxanes: Paclitaxel/Docetaxel**
Paclitaxel concurrently administered with WBRT and combined with cisplatin every 3 weeks is a feasible treatment schedule for patients with brain-metastasized NSCLC, without evidence for inducing significant neurotoxicity. This study did not score for QoL [30].

To our knowledge, no published clinical trials have administered docetaxel, alone or in a multiagent chemotherapy schedule, concurrently with cranial radiotherapy for the treatment of brain metastases.

**Combination of Radiotherapy and Targeted Agents**

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One study described the toxicity (Table 2) of lapatinib (maximum, 1,500 mg once daily) combined with cranial radiotherapy. This trial reported a seizure in one patient. No other grade III or higher neurotoxicity was reported. QoL was scored by using FACT-Br and showed a general decline of QoL after the treatment. However, only a limited number of patients could be tested both at baseline and after finishing treatment [47].
Disease [52]. Additionally, 4 case reports in patients with braingia, intracranial hypertension, convulsion on meningitis, and apha due to radionecrosis in 1 of 12 patients [50]. Another retrospec tive study reported the following symptoms in 6 melanoma patients who developed a seizure. However, it was not clear whether the seizure was caused by tumor progression or by radiation necrosis. No (other) significant toxicity was reported [51]. A third retrospecti ve study reported 1 melanoma patient with brain metastases who also had radiation dermatitis on the radiated site [48]. Two other retrospective studies described possible neurological toxicity, but no high-grade neurotoxicity was reported [49]. A retrospective study also identified symptoms due to radionecrosis in 1 of 12 patients [50]. Another retrospective study reported 1 melanoma patient with brain metastases who developed a seizure. However, it was not clear whether the seizure was caused by tumor progression or by radiation necrosis. No (other) significant toxicity was reported [51]. A third retrospective study reported the following symptoms in 6 melanoma patients with brain metastases: confusion, paresthesia, hemiplegia, intracranial hypertension, convulsion on meningitis, and aphasia. No grading system was used to assess the severity. All these patients had highly metastatic (4–20 brain metastases) cerebral disease [52]. Additionally, 4 case reports in patients with brain metastases from melanoma described no evidence of increased intracranial toxicity with concurrent use of WBRT and vemurafenib [53]. None of these studies assessed neurocognition or QoL.

**Combination of Radiotherapy and Monoclonal Antibodies**

**Immune Checkpoint Inhibitors: Ipilimumab**

Five articles describe toxicity (Table 2) when ipilimumab (3 or 10 mg/kg every 3 weeks) was combined with cranial radiotherapy. One study reported no high-grade neurotoxicity, and QoL (performance status) did not change for 8 of 10 patients [54]. Two studies compared a radiotherapy-only group with a radiotherapy plus ipilimumab group and reported no difference in toxicity [55, 56]. One retrospective study described possibly more intratumoral bleeding with administration of ipilimumab concurrently with radiotherapy. However, this did not require any intervention. This trial also described one patient with grade III cognitive impairment during WBRT. Other reported neurotoxicity was only low grade. QoL was not assessed [57]. Another retrospective study described grade III–IV toxicity in 20% of melanoma patients treated with radiation therapy combined with ipilimumab, including both neurological and non-neurological toxicity. Neurological toxicity included bleeding from treated brain metastasis (grade III and IV) and seizures (grade III). QoL was not assessed [58].

**Trastuzumab**

Two studies reported the toxicity (Table 2) of the combination of trastuzumab (2 mg/kg weekly or 6 mg/kg every 3 weeks) and cranial radiotherapy. One retrospective study reported no high-grade neurotoxicity. QoL was not scored [59]. Another article reported four case reports in which multiple neurological symptoms (headache, nausea/vomiting, speech impairment, short-term memory deficits, imbalance, gait disturbance, and visual deficits) were observed, all of which were attributed to brain edema due to concurrent use of trastuzumab and cranial radiotherapy. The level of neurotoxicity was not scored [60].

**Bevacizumab**

One study evaluated toxicity (Table 2) for the concurrent use of bevacizumab (15 mg/kg three times a month) and cranial radiotherapy for brain metastases. This phase I study reported no high-grade neurotoxicity and did not assess neurocognition and QoL [61].

**Discussion**

Approximately 10%–20% of all solid tumors will eventually metastasize to the brain. NSCLC, small cell lung cancer, breast cancer, melanoma, and RCC are the most common primary tumors that develop brain metastases [8]. Cranial radiotherapy is still the standard treatment of symptomatic brain metastases. There is growing evidence that some systemic anticancer agents may also control brain metastases in selected patients, especially when brain metastases are asymptomatic and relatively small [2]. When brain metastases progress and become symptomatic and unresponsive to the systemic anticancer treatment that is administered to control the extracerebral metastases, a repeated question is whether the systemic treatment should be discontinued at the time of cranial radiotherapy of brain metastases in order to prevent significant neurotoxicity. Instead of long-term discontinuation, a more pragmatic approach can be defended, for example, discontinuation 1 week before to 1 week after the cranial radiotherapy. This approach seemed to be feasible on the basis of the data from a recently published retrospective study, which combined SRS with multiple types of systemic anticancer therapies, without increasing neurotoxicity. However, no information on issues such as treatment schedule and drug dosage was provided [62].

It is obvious that multiple factors should be taken into account in addressing whether to discontinue systemic therapies during cranial radiotherapy. One of these factors is a significant interpatient and intrapatient variation in the intratumoral...
concentration of specific oncolytics in brain metastases due to differences in permeability of the blood-tumor-barrier (BTB) for different anticancer agents and also in the expression of drug efflux pumps, such as P-glycoprotein [63–66]. Table 1 shows these pharmacological characteristics for the different anti-cancer agents.

The trials described in this article do not show increased neurotoxicity for capcitabine, 5-fluorouracil (5-FU), cisplatin and carboplatin, or taxanes when administered concurrently with cranial radiotherapy. This is the case for both monotherapy and also combined in multidrug schedules, commonly used in the palliative treatment of metastasized solid tumors (Table 2). However, it should be taken into account that high-level evidence is lacking. Moreover, data regarding neurocognitive impairment and decreases in QoL are extremely sparse because most studies are retrospective or did not include these data. Also, the methods used to assess neurocognition (e.g., Folstein test) are insensitive and therefore cannot secure a lack of neurocognitive toxicity [67]. On the basis of the available information the chemotherapy regimens containing 5-FU or capcitabine could be continued, when symptomatic brain metastases require treatment with cranial radiotherapy, and only when extracerebral tumor load necessitates protracted systemic treatment.

Combining gemcitabine, at a dose of 700 mg/m², with cranial radiotherapy is not feasible because of a significant increase in neurotoxicity [17]. It is expected that the commonly used schedule of administering gemcitabine at a dose of 1,000 mg/m² will result in clinically significant neurotoxicity when used concurrently with WBRT. The $t_{1/2}$ of gemcitabine is short: 0.7–1.6 hours (Table 1). It is expected that 97% of this drug is eliminated after 8 hours (5 times $t_{1/2}$). Because gemcitabine is also metabolized into active metabolites intra-tumorally, neurotoxicity can still occur when cranial radiotherapy is started after complete drug elimination is reached. There are no data available that define when cranial radiotherapy can be safely started after discontinuing gemcitabine; gemcitabine-induced radiation recall has been described from 3 weeks to 8 months from the time gemcitabine was initiated. According to the available literature, which is sparse and might underestimate the risk for increased neurotoxicity, the concurrent and sequential use of gemcitabine and cranial radiotherapy should be discouraged.

Inhibitors of angiogenesis (e.g., sunitinib and sorafenib) are routinely used to treat metastasized RCC [68]. For patients with symptomatic brain metastases of RCC, combination with cranial radiotherapy did not result in clinically significant neurotoxicity. However, clinical trials included only a small number of patients, and both neurocognitive testing and scoring of QoL were insensitive and therefore not conclusive. Concurrent use of sorafenib, another tyrosine-kinase inhibitor of endothelial growth factor receptor, was associated with significant neurotoxicity when both WBRT and SRS were used [42]. Although high-level evidence is lacking, this combination should be discouraged. The safety of cranial radiotherapy combined with TKIs, used in NSCLC, was recently reviewed by Hendriks et al. [73].

An incidental increase in neurotoxicity has also been reported when other tyrosine kinase inhibitors, such as vemurafenib, are combined with cranial radiotherapy. This is supported by a statement from the manufacturer, in agreement with the European Medicines Agency, which advises caution when vemurafenib is used before, during, or after cranial radiotherapy [74]. A recently published literature review on the combination of BRAF inhibitors and cranial radiotherapy recommends holding BRAF inhibitors for at least 3 days before and after fractional radiotherapy and at least 1 day before and after stereotactic radiosurgery [75].

However, the duration of discontinuation of systemic oncolytics remains a matter of debate.

Ninety-seven percent plasma elimination of these drugs is achieved after 5 times $t_{1/2}$. However, this does not include any remaining metabolic activities of these tyrosine kinase inhibitors intratumorally, as mentioned earlier. Thus, increased neurotoxicity with neurocognitive deterioration and decreased QoL can never be completely prevented, especially because it is not known whether there is a dose-dependent effect for radiosensitization. Therefore, the risks for extracerebral tumor flare after stopping TKI should be weighed against the risks for increased neurotoxicity due to concurrent treatment.
Immune checkpoint modulators, such as ipilimumab, a large monoclonal antibody, are unable to penetrate the BBB in patients without brain metastases (Table 1) [76]. However, in brain metastases the BBB is mostly disrupted, which may facilitate ipilimumab to cross the perivascular space and activate peripherally recruited T cells. Alternatively, ipilimumab-activated T cells in the peripheral circulation may enter the brain metastases through the BBB/BBB. Combining radiation therapy for melanoma brain metastases with ipilimumab appears to be safe and well tolerated. However, a mostly asymptomatic, transient increase of lesion size, suggesting subacute inflammatory response or intratumoral bleeding, was seen in several studies in which SRS was combined with ipilimumab. This pseudoprogression was not present when SRS was given after completion of ipilimumab treatment [58].

Further studies are needed to investigate the ideal sequence of ipilimumab and SRS in order to minimize side effects while maximizing efficacy. Research is also ongoing on whether SRS before or during ipilimumab and potentially other immune checkpoint modulators might increase the immune response by increasing the release of tumor antigens. In addition, one could anticipate an effect on nonirradiated lesions and ultimately the prevention of new metastatic events, the so-called abscopal effect [77, 78].

Other monoclonal antibodies, such as trastuzumab, are also very limited in passing the intact BBB because of their large molecular weight (Table 1). However, trastuzumab can prolong median overall survival in patients with brain metastasized HER2-expressing breast tumors, suggesting its permeation through the BTB [79, 80]. When brain metastases develop during trastuzumab treatment, combination with radiation therapy seems to be safe and feasible.

Conclusion

Brain metastases may develop during systemic treatment schedules that successfully control extracerebral tumor metastases. Cranial radiotherapy is traditionally used to control symptomatic brain metastases. Among all the systemic cancer treatments reviewed, an elevated risk for neurotoxicity was described with gemcitabine, erlotinib, and vemurafenib. However, caution should be used in interpreting these results because most studies are retrospective studies or small phase I trials that performed only limited screening for neurotoxicity. Therefore, no definite conclusions can be made regarding the concurrent use of these oncolytics with cranial radiotherapy on the basis of the data currently available. However, there is growing evidence that not all systemic therapies need to be discontinued during cranial radiotherapy. Prospective randomized trials with overall survival as well as neurorecognition and QoL as endpoints are needed in this palliative patient subset. Immune checkpoint modulators and treatments that activate the immune system are promising. They are being investigated with regard to whether their combination with cranial radiotherapy may improve treatment outcome in the setting of brain metastases to induce an abscopal effect.

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Data analysis and interpretation: Maikel Verduin, Jaap D. Zindler, Hanneke M.A. Martinussen, Rob L.H. Jansen, Sander Croes, Lizza E.L. Hendriks, Danielle B.P. Eekers, Ann Hoeben

Manuscript writing: Maikel Verduin, Hanneke M.A. Martinussen, Ann Hoeben

Final approval of manuscript: Maikel Verduin, Jaap D. Zindler, Hanneke M.A. Martinussen, Rob L.H. Jansen, Sander Croes, Lizza E.L. Hendriks, Danielle B.P. Eekers, Ann Hoeben

REFERENCES


Chemoradiation for Cerebral Metastases


